525 Rec'd PCT/PTO 30 NOV 2000

Form PTO-1390

U S DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
TUR-101

U.S. APPLICATION NO.
09/701547

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/FI99/00511 | June 11, 1999 | June 30, 1998 |

TITLE OF INVENTION:
A MEMBRANE OR MATRIX FOR CONTROLLING THE PERMEATION RATE OF DRUGS

DATE:
November 30, 2000

APPLICANT(S) FOR DO/EO/US
Harri JUKARAINEN, Tommi MARKKULA, Juha ALA-SORVARI, Matti LEHTINEN and Jarkko RUOHONEN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information

1. [XX] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. [XX] This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C 371(b) and PCT Articles 22 and 39(1).

4. [XX] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [XX] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [XX] has been transmitted by the International Bureau.
   c [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [XX] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [XX] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [XX] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [XX] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern other document(s) or information included:**

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [XX] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [XX] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [XX] Other items or information:

    a WO 00/00550
    b. International Preliminary Examination Report(PCT/IPEA/409)
    c. International Search Report (PCT/ISA/210)

525 Rec'd PCT/PTO 30 NOV 2000

| U.S. Application No | International Application No. | Attorney's Docket No. |
|---|---|---|
| 09/701547 | PCT/FI99/00511 | TUR-101 |

17. [XX] The following fees are submitted:

| | CALCULATIONS | PTO USE ONLY |
|---|---|---|
| **Basic National Fee (37 CFR 1.492(a)(1)-(5)):** Search Report has been prepared by the EPO or JPO. . . . . **$860.00** | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) **$690.00** | | |
| No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . . . **$710.00** | | |
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . . . **$1,000.00** | 1,000.00 | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4). . . . . **$100.00** | | |
| **ENTER APPROPRIATE BASIC FEE AMOUNT** = | $ 1,000.00 | |
| Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ | |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total claims | 22-20 | 2 | 0 x $ 18.00 | $ 36.00 | |
| Indep. claims | 1 - 3 | 0 | 0 x $ 80.00 | $ | |
| Multiple dependent claim(s) (if applicable) | | | + $270.00 | $ | |
| | | | **TOTAL OF ABOVE CALCULATIONS** = | $ 1,036.00 | |
| Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28). | | | | $ | |
| | | | **SUB TOTAL** = | $ 1,036.00 | |
| Processing fee $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | | | $ | |
| | | | **TOTAL NATIONAL FEE** = | $ 1,036.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property + | | | | $ 40.00 | |
| | | | **TOTAL FEES ENCLOSED** = | $ 1,076.00 | |
| | | | | Amount to be: refunded | $ |
| | | | | charged | $ |

a. [XX] Checks in the amount of $1,036.00 and $40 to cover the above fee are enclosed.

b. [ ] Please charge my Deposit Account No. 50-1258 in the amount of $_____ to cover the above fees. Two copies of this sheet are enclosed.

c. [xx] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1258. Two copies of this sheet are enclosed.

NOTE: **Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

James C Lydon
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314

James C. Lydon
Signature

James C. Lydon
Name

30,082
Registration Number

November 30, 2000
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the National Stage Application of:

**Attn: Box PCT**

International Application No. PCT/FI99/00511

Harri JUKARAINEN et al.

I.A. Filing Date: June 11, 1999

U.S. Filing Date: November 30, 2000

U.S. Serial Number: Not Yet Assigned

For: A MEMBRANE OR MATRIX FOR CONTROLLING THE PERMEATION RATE OF DRUGS

**PRELIMINARY AMENDMENT**

Commissioner for Patents
Washington, D.C. 20231

November 30, 2000

Sir:

Prior to calculation of the filing fee, please amend the application as follows:

**IN THE CLAIMS:**

Please amend claims 3, 4, 6, 12, 14, 16, 17, 20 and 22 as follows:

Claim 3, line 1, delete "or 2".

Claim 4, line 1, delete "or 3".

Claim 6, line 1, delete "or 3".

Claim 12, line 1, delete "or 11".

Claim 14, line 1, delete "or 11".

Claim 16, line 1, delete "any of Claims 10 -"; and
line 2, change "15" to --Claim 10--.

Claim 17, line 1, delete "any of Claims 1 -"; and
line 2, change "16" to --Claim 1--.

Claim 20, line 1, delete "or 19".

Claim 22, line 1, change "any of Claims 18 - 21" to --Claim 18--.

IN THE ABSTRACT:

Please insert the attached Abstract after the claims.

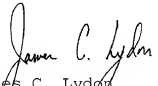
**REMARKS**

This Preliminary Amendment amends claims 3, 4, 6, 12, 14, 16, 17, 20 and 22 by eliminating multiple dependencies, and inserts a new Abstract based on the PCT Abstract. Claims 1-22 are pending.

Prompt and favorable examination of the application are earnestly requested.

It is not believed that any fee is required for entry and consideration of this Preliminary Amendment. Nevertheless, the Director is authorized to charge our Deposit Account No. 50-1258 in the amount of any fee deemed necessary for such entry and consideration.

Respectfully submitted,



James C. Lydon
Reg. No. 30,082

Atty. Case No.: TUR-101
100 Daingerfield Road
Suite 100
Alexandria, VA 22314
Telephone: (703) 845-0445
Facsimile: (703) 845-0447

Attachment:
Abstract of the Disclosure

# A MEMBRANE OR MATRIX FOR CONTROLLING THE PERMEATION RATE OF DRUGS

The invention relates to a membrane or matrix intended for controlling the permeation rate of a drug, wherein said membrane or matrix comprises a siloxane-based elastomer composition, and to a method for the preparation of said elastomer composition.

## STATE OF THE ART

Polysiloxanes, in particular poly(dimethyl siloxane) (PDMS), are highly suitable for use as a membrane or matrix regulating the permeation rate of drugs in various drug forms, in particular in implants and IU systems. Polysiloxanes are physiologically inert, and a wide group of drugs are capable of penetrating polysiloxane membranes, which also have the required strength properties.

It is known from the literature that the adding of poly-(ethylene oxide) groups, i.e. PEO groups, to a PDMS polymer may increase the permeation rate of drugs. Publication KL Ullman et al., Journal of Controlled Release 10 (1989) 251-260, describes membranes prepared from a block copolymer which contains PEO and PDMS and the penetration of various steroids through these membranes. It is noted in the publication that an increasing PEO amount in the block polymer tends to increase the penetration of hydrophilic steroids, while the penetration of lipophilic steroids decreases. The block copolymer described in the publication is very complicated in its structure and preparation, and would therefore not be facile in more extensive technical production.

## OBJECT OF THE INVENTION

The object of the invention is to provide an elastomer composition which is easy to prepare, through which a drug

migrates at the desired rate, and which gives the membrane the required mechanical properties.

The object of the invention is in particular to provide an elastomer composition through which the permeation rate of drugs with hormonal action can be controlled.

## SUMMARY OF THE INVENTION

The invention thus relates to a membrane or matrix intended for controlling the permeation rate of a drug, said membrane or matrix comprising a siloxane-based elastomer composition comprising at least one elastomer and possibly a non-crosslinked polymer. The invention is characterized in that the elastomer composition comprises poly(alkylene oxide) groups and that the poly(alkylene oxide) groups are present in the elastomer or polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said blocks or grafts being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms.

The invention also relates to a method for the preparation of a siloxane-based elastomer which comprises poly(alkylene oxide) groups and is intended for use in a membrane or matrix for controlling the permeation rate of drugs. The method is characterized in that a) a vinyl-functional polymer component and a hydride-functional component are crosslinked in the presence of a catalyst, or that b) a polymer component is crosslinked in the presence of a peroxide catalyst.

## DETAILED DESCRIPTION OF THE INVENTION

### General description of the elastomer composition

The term "elastomer composition" may stand for one single elastomer, in which case the polysiloxane units which contain poly(alkylene oxide) groups are present in the said

elastomer.

According to another embodiment, the elastomer composition may be made up of two elastomers which are interlaced, one inside the other. In this case the first elastomer comprises poly(alkylene oxide) groups so that the poly(alkylene oxide) groups are present in the said elastomer either as alkoxy-terminated grafts of polysiloxane units or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds. The poly(alkylene oxides) may also be present as a blend of the options mentioned. The second elastomer may be a siloxane-based elastomer, suitably a poly(dimethyl siloxane)-based elastomer. The said second elastomer may possibly also comprise poly(alkylene oxide) groups. These poly(alkylene oxide) groups may also be present either as alkoxy-terminated grafts of poly(dimethyl siloxane) units or as blocks, the said grafts or blocks being linked to the poly(dimethyl siloxane) units by silicon-carbon bonds. The poly(alkylene oxides) may also in this elastomer be present as a blend of the options mentioned above.

According to a third embodiment, the elastomer composition may be a blend which comprises a siloxane-based elastomer, which is, for example, made up of PDMS, and at least one straight-chain polysiloxane copolymer which comprises poly(alkylene oxide) groups. In this case the poly(alkylene oxide) groups are present in the said polymer either as alkoxy-terminated grafts of polysiloxane units or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds. The poly(alkylene oxide) groups may, of course, also be present in the polymer as a blend of the forms mentioned. In this embodiment, also the siloxane-based elastomer may comprise poly(alkylene oxide) groups, in which case these poly(alkylene oxide) groups are present in the elastomer either as alkoxy-terminated grafts of polysiloxane units or as blocks, the said blocks or grafts being linked to the

polysiloxane units by silicon-carbon bonds. The poly(alkylene oxide) groups may also be present as a blend of the forms mentioned.

Of course, the elastomer composition may also be made up of two elastomers interlaced one inside the other, as above, and at least one straight-chain polysiloxane copolymer which comprises poly(alkylene oxide) groups.

The poly(alkylene oxide) groups of the elastomer composition may suitably be, for example, poly(ethylene oxide) groups (PEO groups).

The polysiloxane units of the elastomer composition are preferably groups having the formula

$$-(SiR'R''O)_qSiR'R''-$$

where R' and R'' are

- partly free groups, which are the same or different and which are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl groups may be substituted or unsubstituted, or alkoxy-terminated poly(alkylene oxide) groups having the formula

$$-R^3-O-(CH-CH_2-O)_m-alk$$
(R on the CH)

where alk is a lower alkyl group, suitably methyl, R is hydrogen or a lower alkyl, m is 1...30, and $R^3$ is a straight or branched $C_2$ - $C_6$ alkyl group,

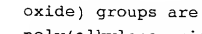
- partly bonds, formed from the hydrogen or alkylene groups, to other polymer chains in the elastomer, and
- possibly partly unreacted groups, such as hydrogen, vinyl or vinyl-terminated alkene, and
- q is 1...3000.

The term "lower alkyl" stands here and generally in the description of the present invention for $C_1$ - $C_6$ alkyl groups.

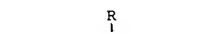
The above-mentioned free R' and R'' groups are suitably a lower alkyl group, preferably methyl.

The term "poly(alkylene oxide) group" means that said group comprises at least two alkyl ether groups successively connected to each other.

According to a preferred embodiment, the poly(alkylene oxide) groups are present in the elastomer in the form of poly(alkylene oxide) blocks having the formula



$$-(CH_2)_yO(\overset{R}{\overset{|}{C}}HCH_2O)_m(CH_2)_y-, \text{ or}$$



$$-CH_2\overset{R_1}{\overset{|}{C}}HCOO(\overset{R}{\overset{|}{C}}HCH_2O)_mCO\overset{R_1}{\overset{|}{C}}HCH_2-$$

where R is hydrogen, a lower alkyl or a phenyl, $R_1$ is hydrogen or a lower alkyl, y is 2...6, and m is 1...30.

The elastomer composition suitably contains a filler, such as silica, in order that the membrane should obtain a sufficient strength.

The word "membrane" means the same as film.

**General description of the method for the preparation of the elastomer composition**

According to a preferred embodiment, the novel elastomer is prepared by crosslinking, in the presence of a catalyst, a vinyl-functional polymer component and a hydride-functional siloxane component.

By crosslinking is meant the addition reaction of the hydride-functional siloxane component with the carbon-carbon double bond of the vinyl-functional polymer

component.

According to another embodiment, the elastomer is prepared by crosslinking the polymer in the presence of a peroxide catalyst. In this case the vinyl and methyl groups react with each other and form carbon-carbon bonds. A crosslink may also be formed between two methyl groups or between two vinyl groups.

For crosslinking, the amounts of the components are preferably selected so that the ratio of the molar amounts of the hydrides and the double bonds is at least 1.

The vinyl-functional polymer component may be

a) a vinyl-functional polysiloxane having the formula

R'-SiR'R''O(SiR'R''O)$_r$SiR'R''R'

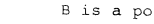
where R' and R'' are the same or different, and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, or

b) an alkenyl terminated polysiloxane-based block copolymer having the formula

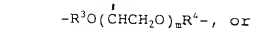
T(AB)$_x$AT (I), where

A = -(SiR'R''O)$_q$SiR'R''-, where R' and R'' are the same or different and are a lower alkyl group, or a phenyl, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula



$$-R^3O(\underset{R}{C}HCH_2O)_mR^4-, \text{ or}$$



$$-CH_2\underset{R_1}{C}HCOO(\underset{R}{C}HCH_2O)_m\underset{R_1}{C}OCHCH_2-,$$

and T is

$$R^1O(\underset{R}{C}HCH_2O)_mR^3-, \text{ or}$$



$$CH_2=\underset{R_1}{C}COO(\underset{R}{C}HCH_2O)_m\underset{R_1}{C}OCHCH_2-$$

where

R is hydrogen, a lower alkyl or phenyl, $R_1$ is hydrogen or a lower alkyl, $R^3$ and $R^4$ are the same or different and are straight-chain or branched $C_2$ - $C_6$ alkylene groups, $R^1$ is a straight-chain or branched $C_2$ - $C_6$ alkenyl group, m is 1...30, q is 1...3000, and x is 0...100, or

c) a vinyl-functional polysiloxane copolymer having the formula



$$R'-SiR'R''O(SiR'R''O)_r(SiR'R''O)_pSiR'R''-R'$$

- where in the first block R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, and

- where in the second block R' is a lower alkyl group, or an alkoxy-terminated poly(alkylene oxide) group having the formula

$-R^3-O-(\underset{\displaystyle R}{\underset{|}{CH}}-CH_2-O)_m-alk$, where alk is a lower alkyl group, suitably methyl, R is hydrogen or a lower alkyl group, $R^3$ is a straight or branched $C_2$ - $C_6$ alkyl, and m is 1...30, or R' is a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and R'' is a lower alkyl or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and p is 1...5000, or

d) α,ω-dialkenyl poly(alkylene oxide) having the formula

$R^1-O-(\underset{\displaystyle R}{\underset{|}{CH_2CH_2O}})_m-R^2$

where $R^1$ and $R^2$ are the same or different straight-chain or branched $C_2$ - $C_6$ alkenyl groups, R is hydrogen or a lower alkyl, and m is 1...30, or

e) a blend of at least two of the above-mentioned components a) - d).

If the formula of the vinyl-functional polysiloxane copolymer is, in accordance with the above description, $R'-SiR'R''O(SiR'R''O)_r(SiR'R''O)_pSiR'R''-R'$, it should be noted that the formula is a kind of gross formula, in which the blocks in successive parentheses may appear in any order in relation to one another. Furthermore, it is preferable that both a vinyl group and the above-mentioned alkoxy-terminated poly(alkylene oxide) group are not bonded to one and the same Si atom.

The hydride-functional component may be

a) a hydride-functional siloxane, which may be straight-chain, star shaped, branched or cyclic, or

b) a hydride-terminated siloxane-based block copolymer

having the formula

$T(BA)_xBT$ (II), where

T = H-SiR'R''O(SiR'R''O)$_q$SiR'R''-,

A = -SiR'R''O(SiR'R''O)$_q$SiR'R''-, where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula

$-R^3-O(\underset{\displaystyle R}{\underset{|}{C}}HCH_2O)_mR^4-$, or

$$-CH_2\underset{\displaystyle R_1}{\underset{|}{C}}HCOO(\underset{\displaystyle R}{\underset{|}{C}}HCH_2O)_m\underset{\displaystyle R_1}{\underset{|}{C}}OCHCH_2-$$

where R is hydrogen, a lower alkyl or a phenyl, $R_1$ is hydrogen or a lower alkyl, $R^3$ and $R^4$ are the same or different and are straight-chain or branched $C_2$ - $C_6$ alkyl groups, m is 1...30, q is 1...3000, and x is 0...100, or

c) a blend of the above-mentioned components a) and b).

According to one embodiment, the hydride-functional siloxane copolymer may be straight-chain, in which case its formula is

R'-SiR'R''O(SiR'R''O)$_r$SiR'R''R'

where R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by hydrogen, and r is 1...27000.

The vinyl-functional polymer component may contain a filler, suitably silica.

The catalyst to be used in the crosslinking is suitably a noble metal catalyst, most commonly a platinum complex in alcohol, xylene, divinyl siloxane or cyclic vinyl siloxane. An especially suitable catalyst is a Pt(0)-divinyl-tetramethyl disiloxane complex.

The elastomer composition made up of two elastomers is prepared so that initially a first elastomer is formed, whereafter a second elastomer is formed by crosslinking in the presence of the first elastomer. Thus the second elastomer will penetrate through the first elastomer.

The elastomer composition which comprises an elastomer and a straight-chain polymer is prepared, for example, by blending a vinyl-functional polymer component, a hydride-functional component, and a polymer which has no vinyl or hydride groups. In the crosslinking, the vinyl-functional polymer component and the hydride-functional component form an elastomer, but the polymer component which does not contain the said functional groups will not take part in the crosslinking reaction but will remain, in a straight-chain form, inside the elastomer.

EXPERIMENTAL SECTION

The invention is described below in greater detail with the help of examples.

Elastomer compositions of different types (A - J) were prepared. Of most composition types there were prepared different compositions which differed one from another with respect to the PEO amount. Elastomer membranes representing the different compositions were tested with respect to the permeation rates of various drugs.

Elastomer compositions prepared

In the elastomer compositions A - H described below, an addition reaction between vinyl groups and silyl hydride groups was used for the crosslinking, i.e. for producing a network structure. The hydride-functional siloxane polymer serving as the crosslinking agent contained at least two Si-H groups, which reacted with the carbon-carbon double bond of the polymer to be crosslinked. Membranes made from elastomer compositions I and J were prepared by using peroxide as the catalyst for crosslinking, in which case the vinyl or methyl groups reacted, forming carbon-carbon bonds. In all the composition types except composition types A, D, F and H, there was first prepared a basic polymer blend, in which case all of the vinyl-containing polymers and the fillers, or vinyl-containing polymers which contained a filler, were mixed together. The filler used was silica. Composition types A, D, F and H had only one vinyl-containing polymer each, and thus they themselves were basic polymers. The basic polymer blend was divided into portions I and II. The catalyst was added to portion I and the crosslinking agent and the inhibitor to portion II. Portions I and II were combined immediately before the crosslinking. The obtained blend was crosslinked at a temperature which was higher than the decomposition temperature of the inhibitor and at which the crosslinking reaction took place at the desired velocity.

A blend can be made of the compositions also directly in one step, in which case the ingredients can be added in the following order: vinyl-containing polymers, inhibitor, catalyst and crosslinking agent.

The following table describes elastomer membranes of different composition types and their initial components.

Table 1

| Composition type | Polymers containing vinyl groups in the basic polymer blend | Crosslinking agent |
|---|---|---|
| A | α,ω-divinyl ether poly(ethylene oxide)-poly(dimethyl siloxane) multi-block copolymer (PEO-(-PDMS-PEO)$_n$) | Hydride-functional siloxane |
| B | PEO-(PDMS-PEO)$_n$ and a siloxane polymer containing a filler | Hydride-functional siloxane |
| C | PEO-(PDMS-PEO)$_n$ together or separately with a siloxane polymer which does or does not contain a filler | α,ω-bis(dimethyl silyl hydride)-poly(dimethyl siloxane)-poly(ethylene oxide) multi-block copolymer (PDMS-(PEO-PDMS)$_n$) together or separately with a hydride-functional siloxane. |
| D | α,ω-divinyl ether poly(ethylene oxide (PEODIVI) | Hydride-functional siloxane |
| E | PEODIVI and a siloxane polymer which does or does not contain a filler | Hydride-functional siloxane |
| F | PEO-grafted dimethyl siloxane-methyl vinyl siloxane copolymer (PDMS-PEO graft copolymer) | Hydride-functional siloxane |
| G | PDMS-PEO graft copolymer and a siloxane polymer which does or does not contain a filler | Hydride-functional siloxane |
| H | α,ω-diallyl ether poly(ethylene oxide)-poly(dimethyl siloxane) multi-block copolymer (APEO-(-PDMS-APEO)$_n$) | Hydride-functional siloxane |
| I | PEO-(PDMS-PEO)$_n$ and a siloxane polymer which does or does not contain a filler | Peroxide |
| J | PDMS-PEO graft copolymer together or separately with a siloxane polymer which does or does not contain a filler | Peroxide |

EXAMPLE 1

Elastomer membrane prepared from composition type A

Ingredients used for the preparation of the elastomer membrane:

- α,ω-divinyl ether PEO-PDMS block copolymer where the amount of PEO was 27.0 % by weight and the vinyl content was 0.186 mmol/g.

- Platinum catalyst Silopren U Katalysatoren Pt-D (Bayer AG), which had a platinum-siloxane complex in a vinyl-containing siloxane matrix. The platinum content was 1 % by weight and the vinyl content was 0.5 mmol/g.

- Crosslinking agent α,ω-di(trimethyl silyl) dimethyl siloxane-hydromethyl siloxane (DMS-HMS) copolymer Silopren U Vernetzer 730 (Bayer AG) having a Si-H content of 7.1 mmol/g, a molar mass of 2800 g/mol and a DMS group to HMS group ratio of 1:1.

- Inhibitor 1-ethinyl-1-cyclohexanol (ETCH, Aldrich) having a decomposition temperature of +40 °C.

The PEO(-PDMS-PEO)$_n$ which was used as the initial substance was prepared as follows:

50 g of anhydrous α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) having a molar mass of 268 g/mol was weighed into a three-necked flask. In addition, 129.87 g of α,ω-bis(dimethyl silyl hydride) poly(dimethyl siloxane) (PDMSDIH, $M_n$ = 717 g/mol) and 30 % by weight of toluene dried by distillation were weighed into the same vessel. Since vinyl groups were present in excess (3 %) in the reaction, in the final product vinyl groups were obtained at both ends, which was essential for the subsequent crosslinking. The reaction solution was stirred over a

magnetic stirring plate at 200 rpm, and dry oxygen was directed through the solution in order to prevent the deactivation of the catalyst. The reaction solution was heated to 50 °C, whereafter the catalyst (Pt(0) divinyltetramethyl disiloxane complex) was added to the solution through the septum. The amount of platinum was 30 ppm, calculated from the amount of reactants. Thereafter the polymerization was monitored by means of IR until the reactions were complete (loss of the Si-H peak at 2130 $cm^{1}$), which took approximately 4 h. After the polymerization, the toluene was distilled off from the solution by raising the temperature to 65 °C and by lowering the pressure to 5 mbar for a period of 1 h.

In the preparation of the elastomer, two blends were first prepared, portions I and II. Portion I contained PEO-(PDMS-PEO)$_n$ and the platinum catalyst. Portion II contained PEO-(PDMS-PEO)$_n$, the crosslinking agent and the inhibitor. Portions I and II were combined by mixing immediately before the crosslinking.

The amounts of the ingredients in the composition example in the final blend to be crosslinked were as follows:

- Basic polymer PEO-(PDMS-PEO)$_n$ 94.87 % by weight
- Platinum catalyst 0.1 % by weight
- Crosslinking agent 5.00 % by weight
- Inhibitor 0.03 % by weight

Portion I was prepared using a chamber mixer. 5.489 g of the basic polymer and 0.011 g of the platinum catalyst were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

The crosslinking agent and the inhibitor were combined before being mixed with portion II. The mixture of the crosslinking agent and the inhibitor was prepared by weighing 0.059 g of ETCH and 9.941 g of Silopren U

Vernetzer 730 into a glass vessel and by stirring the mixture in a water bath of +37 °C until ETCH had dissolved completely in the crosslinking agent. The amount of inhibitor in the mixture was 0.59 % by weight.

Portion II was prepared using a chamber mixer. The mantle of the chamber mixer was cooled by water circulation to a point below room temperature, whereupon the temperature increase due to friction did not raise the temperature to the decomposition temperature of the inhibitor. 4.947 g of PEO-PDMS block copolymer and 0.553 g of the mixture of the crosslinking agent and the inhibitor were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

Portions I and II were combined immediately before the crosslinking, by adding 5 grams of portion I and 5 grams of portion II into the mixing chamber of the chamber mixer. The ingredients were agitated until the blend was homogeneous. The blend was recovered and was drawn into vacuum to remove air bubbles. Four batches of 2 g of the blend were weighed and crosslinked successively in a hot-press.

The weighed blend was placed between two FEP release membranes in the center of a round metal form having a thickness of 0.4 mm and an inner diameter of 8 cm. The blend, together with the forms and the FEP membranes, was placed between the compression surfaces of the hot-press, which surfaces had been heated in advance to +115 °C. The surfaces were pressed together and were kept pressed at a pressure of 200 bar for 5 minutes. The pressure was released and the membrane was allowed to set at room temperature for 24 hours. Round test pieces having a diameter of 22 mm were cut out from the membranes by means of a puncher.

EXAMPLE 2

Elastomer membrane prepared from composition type B

Ingredients used for the preparation of the elastomer membrane:

- The PEO(-PDMS-PEO)$_n$ was the same as in Example 1, except that the amount of PEO had been increased to 28.0 % by weight and the vinyl content to 0.24 mmol/g by increasing the proportion of PEODIVI in the synthesis of the block copolymer.

- The catalyst, the crosslinking agent and the inhibitor were the same as in Example 1.

The siloxane polymer which contained filler was a dimethyl siloxane-vinyl methyl siloxane (DMS-VMS) copolymer containing a silica filler and having a molar mass of $M_n$ = 400,000 g/mol. The vinyl content of the blend was 0.011 mmol/g. There was 36 % by weight of silica mixed in the polymer, and the silica was surface-treated with α,ω-bis(dimethyl hydroxysilyl) poly(dimethyl siloxane) (M = 520 g/mol), which was present in an amount of 12 % by weight in the blend.

The amounts of ingredients in the composition example were as follows:

- PEO(-PDMS-PEO)$_n$ 32.8 % by weight
- DMS-VMS copolymer containing a silica filler, 60.9 % by weight
- Platinum catalyst 0.1 % by weight
- Crosslinking agent 6.19 % by weight
- Inhibitor 0.03 % by weight

First the basic polymer blend was prepared in a chamber mixer. 4.2 grams of the PEO(-PDMS-PEO)$_n$ block copolymer and

7.8 grams of the DMS-VMS copolymer containing a silica filler were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

Portion I was prepared as in Example 1.

The combining of the crosslinking agent and the inhibitor was done, as in Example 1, before mixing with portion II, except that ETCH was weighed in an amount of 0.048 g and Silopren U Vernetzer 730 in an amount of 9.952 g. The amount of inhibitor in the blend was 0.48 % by weight.

Portion II was prepared as in Example 1, except that the basic polymer blend was weighed in an amount of 4.816 grams and the mixture of the crosslinking agent and the inhibitor in an amount of 0.684 grams.

Portions I and II were combined as in Example 1. Four batches of 2.1 g of the blend were weighed and were crosslinked successively in a hot-press, as in Example 1.

EXAMPLE 3

**Elastomer membrane prepared from composition type C**

Ingredients used for the preparation of the elastomer membrane:

- The PEO(-PDMS-PEO)$_n$ was the same as in Example 2. The catalyst and the inhibitor were the same as in Examples 1 and 2.

- The dimethyl siloxane-vinyl methyl siloxane (DMS-VMS) copolymer containing a silica filler was the same as in Example 2.

- The crosslinking agent used was a PDMS-(-PEO-PDMS)$_n$ copolymer having a Si-H content of 0.26 mmol/g, and the

amount of PEO in it was 23.6 % by weight.

The said crosslinking agent was prepared as follows:

40 g of an anhydrous α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) having a molar mass of 246.3 g/mol was weighed into a three-necked flask. In addition, 129.4 g of α,ω-bis(dimethyl silyl hydride) poly(dimethyl siloxane) (PDMSDIH, $M_n$ = 717 g/mol) and 30 % by weight of toluene dried by distillation were weighed into the same vessel. Since dimethyl silyl hydride groups were present in excess (10 %) in the reaction, dimethyl silyl hydride groups were obtained at both ends in the final product. The reaction solution was stirred over a magnetic stirring plate at 200 rpm, and dry oxygen was directed through the solution to prevent the deactivation of the catalyst. The reaction solution was heated to 50 °C, whereafter the catalyst (Pt(0) divinyl-tetramethyl siloxane complex) was added to the solution through the septum. The amount of platinum was 30 ppm, calculated from the amount of the reactants. Thereafter the polymerization was monitored by means of IR until the reactions were complete (loss of the vinyl peak at 1600 $cm^{1}$), which took approximately 4 h. After the polymerization, the toluene was removed from the solution by distillation by raising the temperature to 65 °C and by lowering the pressure to 5 mbar for a period of 1 h.

The amounts of the ingredients in the composition example were as follows:

- PEO(-PDMS-PEO)$_n$ 1.10 % by weight
- DMS-VMS containing a silica filler, 85.50 % by weight
- Platinum catalyst 0.10 % by weight
- Crosslinking agent α,ω-bis-(dimethyl silyl hydride) PEO-PDMS 13.27 % by weight
- Inhibitor 0.03 % by weight

First the basic polymer blend was prepared in a chamber mixer. 0.15 grams of the α,ω-divinyl ether PEO-PDMS block

copolymer and 11.85 grams of the DMS-VMS copolymer containing a silica filler were weighed into the mixing chamber. The ingredients were agitated until the blend was homogeneous.

Portion I was prepared as in Example 1. The combining of the crosslinking agent and the inhibitor was done, as in Example 1, before mixing with portion II, except that ETCH was weighed in an amount of 0.022 g and PDMS-$(PEO-PDMS)_n$ block copolymer in an amount of 9.978 g instead of Vernetzer 730. The amount of inhibitor in the blend was 0.22 % by weight.

Portion II was prepared as in Example 1, except that the basic polymer blend was weighed in an amount of 4.04 grams and the mixture of the crosslinking agent and the inhibitor in an amount of 1.46 grams.

Portions I and II were combined as in Example 1. Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 4

**Elastomer membrane prepared from composition type D**

Ingredients used for the preparation of the elastomer membrane:

- α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) (poly-ethylene glycol divinyl ether, Aldrich, $M_n$ = 240 g/mol). The vinyl amount obtained by titration was 7.4 mmol/g.

- Catalyst Gelest SIP 6831.0, platinum-siloxane complex in xylene, platinum content 2.25 % by weight.

- The crosslinking agent and the inhibitor were the same as in Example 1.

The amounts of the ingredients in the composition example were as follows:

- PEODIVI 52.231 % by weight
- Platinum catalyst 0.045 % by weight
- Crosslinking agent 47.694 % by weight
- Inhibitor 0.030 % by weight

First a mixture of the crosslinking agent and the inhibitor was prepared as in Example 1, except that the inhibitor was weighed in an amount of 0.0063 grams and the crosslinking agent in an amount of 9.9937 grams. The amount of inhibitor in the mixture was 0.063 % by weight.

5.2231 grams of PEODIVI and 0.0045 grams of the platinum catalyst were mixed together in a glass vessel. 4.772 grams of the mixture of the crosslinking agent and the inhibitor was mixed into it.

Eight batches of 0.8 g of the blend were weighed into flat-bottomed aluminum forms having a diameter of 5 cm and having a FEP membrane on the bottom. The forms were placed under a 100 mbar vacuum at +115 °C for a period of 15 minutes. Test pieces were cut out from the elastomer obtained.

EXAMPLE 5

**Elastomer membrane prepared from composition type E**

Ingredients used for the preparation of the elastomer membrane:

- PEODIVI, the same as in Example 4.
- DMS-VMS copolymer, the same as in Example 2.

The catalyst, the crosslinking agent and the inhibitor were the same as in Example 1.

The amounts of the ingredients in the composition example were as follows:

- PEODIVI 11.37 % by weight
- DMS-VMS copolymer 64.46 % by weight
- Platinum catalyst 0.1 % by weight
- Crosslinking agent 24.03 % by weight
- Inhibitor 0.03 % by weight

First, a mixture of the crosslinking agent and the inhibitor was prepared, as in Example 1, except that the inhibitor was weighed in an amount of 0.0125 grams and the crosslinking agent in an amount of 9.9875 grams. The amount of inhibitor in the mixture was 0.125 % by weight.

1.138 grams of PEODIVI and 6.446 grams of DMS-VMS copolymer were mixed together in a chamber mixer. 0.01 grams of platinum catalyst was added, and the blend was agitated until homogeneous. 2.406 grams of the mixture of the crosslinking agent and the inhibitor was added and the blend was agitated until homogeneous.

Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 6

**Elastomer membrane prepared from composition type F**

Ingredients used for the preparation of the elastomer membrane:

- PDMS-PEO graft copolymer having a vinyl concentration of 0.0743 mmol/g and a PEO content of 1.28 % by weight.

- The catalyst, the crosslinking agent and the inhibitor were the same as in composition A.

The PDMS-PEO graft copolymer used was prepared as follows:

600 g of octamethyl cyclotetrasiloxane ($D_4$), 9.28 g of poly-(dimethyl siloxane)-poly(ethylene oxide) graft copolymer (Gelest, DBE-821, containing 80 % by weight PEO), 6.18 g of dimethyl vinyl silyl end-blocked PDMS (end-blocker, Bayer Silopren U2), and 3.1 g of tetramethyl tetravinyl cyclotetrasiloxane were weighed. The reactor was nitrogenated, the weighed chemicals were poured in, and stirring was started. The inside temperature of the reactor was raised to 135 °C, and the catalyst (potassium siloxanolate, 0.9 ml, 20 ppm $K^+$) was added to the reaction solution. The viscosity of the reaction solution began to increase vigorously, and at 1 h from the adding of the catalyst it was possible to deactivate the catalyst by increasing the reactor pressure to 2 bar for a period of 15 minutes by means of carbon dioxide. Thereafter the light cyclic compounds (13 % by weight) were removed from the reaction solution by distillation (10 mbar, 30 min, 135 °C). Product $M_n$ = 190,000 g/mol.

The amounts of the ingredients in the composition example were as follows:

- Basic polymer PDMS-PEO graft copolymer 96.10 % by weight
- Platinum catalyst 0.5 % by weight
- Crosslinking agent 3.06 % by weight
- Inhibitor 0.34 % by weight

The combining of the crosslinking agent and the inhibitor was done as in Example 1, except that ETCH was weighed in an amount of 1.0 g and Silopren U Vernetzer 730 in an amount of 9.0 g. The amount of inhibitor in the mixture was 10 % by weight.

9.61 grams of the PDMS-PEO graft copolymer and 0.05 grams of the platinum catalyst were mixed together. 0.34 grams of the mixture of the crosslinking agent and the inhibitor was

added and the blend was stirred until homogeneous.

Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 7

**Elastomer membrane prepared from composition type G**

Ingredients used for the preparation of the elastomer membrane:

- The PDMS-PEO graft copolymer was the same as in Example 6.
- The DMS-VMS copolymer was the same as in Example 2.
- The catalyst, the crosslinking agent and the inhibitor were the same as in Example 1.

The amounts of the ingredients in the composition example were as follows:

- PDMS-PEO graft copolymer 26.75 % by weight
- DMS-VMS copolymer 72.31 % by weight
- Platinum catalyst 0.10 % by weight
- Crosslinking agent 0.81 % by weight
- Inhibitor 0.03 % by weight

The combining of the crosslinking agent and the inhibitor was done as in Example 1, except that ETCH was weighed in an amount of 0.36 g and Silopren U Vernetzer 730 in an amount of 9.64 g. The amount of inhibitor in the mixture was 3.6 % by weight.

2.675 grams of the PDMS-PEO graft copolymer and 7.231 grams of the DMS-VMS copolymer containing a filler were mixed together. 0.01 grams of the platinum catalyst was added and the blend was stirred until homogeneous. 0.084 grams of the mixture of the crosslinking agent and the inhibitor was

added and the blend was stirred until homogeneous.

Four batches of 2.1 g of the blend were weighed and were successively crosslinked in a hot-press, as in Example 1.

EXAMPLE 8

**Elastomer membrane prepared from composition type H**

Ingredients used for the preparation of the elastomer membrane:

- APEO-(-PDMS-APEO)$_n$, where the amount of PEO was 10.3 % by weight and the vinyl content 0.063 mmol/g.
- The catalyst was the same as in Example 4.
- The inhibitor was the same as in Example 1.

- The crosslinking agent was a DMS-HMS copolymer which contained 22.5 % by weight methyl hydride siloxane groups (Gelest).

The APEO-(-PDMS-APEO)$_n$ used was prepared as follows:

Anhydrous α,ω-diallyl poly(ethylene oxide) (PEODIAL) which had a molar mass of 520 g/mol and which was prepared by adapting the procedure disclosed in the publication Mei-Hui, Yang, Laing-Jong, Li, and Tsang-Feng, Ho, Synthesis and Characterization of polymethylsiloxane/poly(ethylene glycol)monomethyl ether copolymers, J. Ch. Colloid & Interface Soc. 3(17), 1994, 19-28 and α,ω-bis(dimethyl silyl hydride) poly(dimethyl siloxane) (PDMSDIH, $M_n$ = 6000 g/mol) were weighed into a three-necked flask. The mass of the PEODIAL was 1.38 g ($M_n$ = 520 g/mol, 5.28 mmol of allyl groups) and the mass of PDMSDIH was 12 g (4.8 mmol of hydride groups), the amount of allyl groups being 10 % greater than that of hydride groups. Thus an α,ω-diallyl-end-blocked final product was ensured.

In addition, toluene was weighed into the reaction vessel in an amount of 45 % by weight (7.2 g). The reaction mixture was stirred over a magnetic stirring plate at 200 rpm, and dry oxygen was bubbled through the mixture in order to prevent the deactivation of the catalyst. The temperature of the reaction mixture was raised to 60 °C. Thereafter the catalyst (Pt(0) divinyl tetramethyl disiloxane complex) was added to the reaction solution through the septum, cautiously one drop at the time. The amount of platinum was 50 ppm, calculated from the reactants. The polymerization was allowed to proceed for approximately 6 h, whereafter the completion of the polymerization was confirmed by IR (loss of the Si-H peak at 2130 $cm^{-1}$). For the removal of the toluene by distillation, the temperature was raised to 65 °C and the pressure was lowered to 5 mbar for a period of 30 min.

The amounts of the ingredients of the composition example were as follows:

- APEO-(-PMDS-APEO)$_n$ 94.68 % by weight
- Platinum catalyst 0.5 % by weight
- Crosslinking agent 4.7 % by weight
- Inhibitor 0.12 % by weight

3.0 grams of the APEO-(-PMDS-APEO)$_n$, 0.0158 grams of the catalyst, 0.0038 g of the inhibitor, and 0.1489 g of the crosslinking agent were mixed together. The air bubbles were removed from the mixture, and the mixture was crosslinked in a hot-press at 110 °C for 15 minutes and was cured at 110 °C for 15 minutes.

EXAMPLE 9

**Elastomer membrane prepared from composition type I**

Ingredients used for the elastomer membrane:
- PEO-(PDMS-PEO)$_n$, where the amount of PEO was 5.0 % by

weight and the vinyl content was 0.04 mmol/g.
- The DMS-VMS copolymer containing a silica filler was the same as in Example 2.
- Dichlorobenzoyl peroxide (Perkadox PD50 S, Nusil).

The PEO-(PDMS-PEO)$_n$ used was prepared as follows:

0.528 g of anhydrous α,ω-divinyl ether poly(ethylene oxide) (PEODIVI) having a molar mass of 240 g/mol was weighed into a three-necked flask. 10 g of α,ω-bis(dimethyl silyl hydride)poly(dimethyl silyl siloxane) (PDMSDIH) having a molar mass of 6000 g/mol was weighed into the same vessel. The PDMSDIH contained hydride groups in an amount of 0.04 % by weight, and thus the amount of hydride groups in 10 grams was 4 mmol and the amount of PEODIVI vinyl groups was 4.4 mmol. Since the vinyl groups were present in excess (10 %) in the reaction, vinyl groups were obtained at both ends of the final product, a fact essential for the subsequent crosslinking. In addition, to facilitate mixing and to prevent the reaction from occurring too vigorously, toluene dried by distillation was added to the reaction mixture so that the proportion of toluene was 30 % by weight (4.5 g). The reaction solution was stirred over a magnetic stirring plate at 200 rpm, and dry oxygen was directed through the solution; this prevented the catalyst from converting to metallic form and thus prevented the deactivation of the catalyst. The reaction solution was heated to 50 °C, whereafter the catalyst (Pt(0) divinyl tetramethyl disiloxane complex) was added to the mixture through the septum. The amount of platinum was 50 ppm, calculated from the amount of the reactants. The catalyst was added dropwise, whereby hot spots in the reactor were avoided. After the adding of the catalyst the reaction was allowed to proceed for 2 h. Thereafter the completion of the reaction was confirmed by IR (loss of the Si-H peak at 2130 $cm^{-1}$). After the polymerization the reaction mixture was heated to 65 °C and the toluene was removed by vacuum distillation (5 mbar) in the course of 30 minutes.

The amounts of ingredients in the composition example were as follows:

- PEO-(PDMS-PEO)$_n$, 4.9 % by weight
- silica-filled DMS-VMS copolymer, 93.9 % by weight
- dichlorobenzoyl peroxide (Perkadox PD50 S, Nusil), 1.2 % by weight.

0.5 g of PEO-(PDMS-PEO)$_n$ and 9.5 g of a DMS-VMS copolymer containing a filler were mixed together. 0.12 g of the peroxide catalyst was mixed with the homogeneous blend, and the blend was hardened at a temperature of +115 °C and a pressure of 200 bar for 5 minutes and was cured at +150 °C for 2 hours.

EXAMPLE 10

**Elastomer membrane prepared from composition type J**

Ingredients used for the preparation of the elastomer:

- PDMS-PEO graft copolymer the same as in Example 6
- Dichlorobenzoyl peroxide Perkadox PD50 S, Nusil

The amounts of the ingredients in the composition example were as follows:

- PDMS-PEO graft copolymer 98.8 % by weight
- Dichlorobenzoyl peroxide Perkadox PD50 S 1.2 % by weight

10 grams of the PDMS-PEO graft copolymer and 0.12 grams of Perkadox PD50 S were mixed together. The blend was hardened at a temperature of +115 °C and a pressure of 200 bar for 5 minutes and was cured at +150 °C for 2 hours.

Permeation tests

Various compositions, in which the amount of PEO groups

varied, were prepared of the above-mentioned composition types A - J. Composition types A - G were tested for the permeation rates of various drugs.

The assay apparatus described in the publication Yie W. Chien, Transdermal Controlled Systemic Medications, Marcel Dekker Inc., New York and Basel 1987, page 173, was used in the tests.

The drug fluxes (permeations) through membranes were measured with a two-compartment diffusion cell at 37 °C (side-by-side diffusion cell, Crown Glass Company). The apparatus consisted of two concentric cells (donor and receptor compartments) that were separated by the elastomer membrane to be investigated. The donor and receptor compartments were both jacketed and thermostated by an external circulating bath and each compartment had a magnetic stirrer. A drug solution and solvent (without drug) was added into the donor and the receptor compartments. At each predetermined time interval, samples were withdrawn from the receptor compartment and replaced with the same volume of solvent. The amount of the drug that permeated through the membrane was measured by HPLC. In all measurements, the thickness (0.4 mm) of the membrane and the surface area of the membranes were constant.

In the tests described below, the permeation rates of two different drugs through a 0.4-mm-thick elastomer membrane were measured by using the assay apparatus described above. The tables below show the effect of the concentration of PEO groups (% by weight of the said compositions) on the permeation rates of the different drugs for elastomers prepared from different composition types. The tables show the relative permeation as compared with a commercial crosslinked dimethyl siloxane-vinyl methyl siloxane elastomer ($M_n$ approximately 400,000 g/mol) containing a silica filler.

Drug 1: Levonorgestrel

| Composition type | PEO concentration % by weight | Relative permeation |
|---|---|---|
| comparison | 0 | 1 |
| A | 28.0 | 14.5 |
| B | 3.8 | 1.5 |
| B | 4.1 | 2.0 |
| B | 5.0 | 2.3 |

**Drug 2:** 17-β-Estradiol

| Composition type | PEO concentration % by weight | Relative permeation |
|---|---|---|
| comparison | 0 | 1 |
| A | 11.6 | 21.3 |
| A | 26.4 | 110 |
| B | 7.8 | 13.3 |
| B | 9.8 | 24.4 |
| C | 3.4 | 4.6 |
| D | 52.3 | 90.4 |
| E | 11.4 | 7.7 |
| F | 1.3 | 2.4 |
| G | 0.5 | 1.4 |

The permeation tests performed showed that an increasing concentration of PEO in the membrane increased the permeation rate for each composition type and for each drug tested, regardless of whether the drug concerned was hydrophilic or lipophilic.

An elastomer composition according to the invention is, for example, highly suited for controlling, in implants and in intrauterine and intravaginal devices, the permeation rates of drugs having hormonal action.

The most important drugs having hormonal action include antiprogestins, progestins, estradiols and androgens.

The above embodiments of the invention are only examples of the implementation of the idea of the invention. For a person skilled in the art it is clear that the different embodiments of the invention may vary within the framework of the claims presented below.

CLAIMS

1. A membrane or matrix for controlling the permeation rate of a drug, said membrane or matrix comprising a siloxane-based elastomer composition comprising at least one elastomer and possibly a non-crosslinked polymer, characterized in that the elastomer composition comprises poly(alkylene oxide) groups, and that the poly(alkylene oxide) groups are present in the elastomer or polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms.

2. The membrane or matrix according to Claim 1, characterized in that the elastomer composition is an elastomer made up of polysiloxane units which comprise poly(alkylene oxide) groups.

3. The membrane or matrix according to Claim 1 or 2, characterized in that the poly(alkylene oxide) groups are poly(ethylene oxide) groups (PEO groups).

4. The membrane or matrix according to Claim 2 or 3, characterized in that the formula of the polysiloxane groups is

$-(SiR'R''O)_qSiR'R''-$

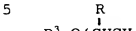
where R' and R'' are
- partly free groups, which are the same or different and which are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, or alkoxy-terminated poly(alkylene oxide) groups having the formula

$$-R^3-O-(\underset{\displaystyle R}{\underset{|}{CH}}-CH_2-O)_n-alk,$$ where alk is a lower alkyl group,

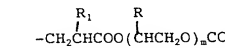
suitably methyl, R is hydrogen or a lower alkyl, $R^3$ is a straight-chain or branched $C_2$ - $C_6$ alkyl, and m is 1...30,
- partly bonds formed from the hydrogen or alkylene groups to other polymer chains in the elastomer, and
- possibly partly unreacted groups, such as hydrogen, vinyl or vinyl-terminated alkene, and
- q is 1...3000.

5. The membrane or matrix according to Claim 4, characterized in that the free R' and R'' groups are a lower alkyl group, preferably methyl.

6. The membrane or matrix according to Claim 2 or 3, characterized in that the poly(alkylene oxide) groups are present in the elastomer in the form of poly(alkylene oxide) blocks having the formula



or



where R is hydrogen, a lower alkyl or phenyl, $R_1$ is hydrogen or a lower alkyl, $R^3$ and $R^4$ are the same or different and are straight-chain or branched $C_2$ - $C_6$ alkyl groups, and m is 1...30.

7. The membrane or matrix according to Claim 1, characterized in that the elastomer composition is made up of two elastomers interlaced one inside the other, in which case
- the first elastomer comprises poly(alkylene oxide) groups, and that the poly(alkylene oxide) groups are present in the said elastomer as alkoxy-terminated grafts of polysiloxane units, or as blocks, in which case the said grafts or blocks are linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms, and

that
- the second elastomer is a siloxane-based elastomer.

8. The membrane or matrix according to Claim 7, characterized in that the second elastomer is a poly(dimethyl siloxane)-based elastomer which possibly comprises poly(alkylene oxide) groups.

9. The membrane or matrix according to Claim 8, characterized in that the possible poly(alkylene oxide) groups of the second poly(dimethyl siloxane)-based elastomer are present in the form of alkoxy-terminated grafts of poly(dimethyl siloxane) units, or as blocks, the said grafts or blocks being linked to the poly(dimethyl siloxane) units by silicon-carbon bonds, or as a mixture of these forms.

10. The membrane or matrix according to Claim 1, characterized in that the elastomer composition is a blend which comprises
- a siloxane-based elastomer and
- a straight-chain polysiloxane copolymer which comprises poly(alkylene oxide) groups, in which case the poly(alkylene oxide) groups are present in the said polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or a mixture of these forms.

11. The membrane or matrix according to Claim 10, characterized in that the poly(alkylene oxide) groups are poly(ethylene oxide) groups (PEO groups).

12. The membrane or matrix according to Claim 10 or 11, characterized in that the formula of the polysiloxane groups is

$-(SiR'R''O)_qSiR'R''-$

where R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, or alkoxy-terminated poly(alkylene oxide) groups having the formula

$-R^3-O-(\underset{R}{CH}-CH_2-O)_m-alk$, where alk is a lower alkyl group, suitably methyl, R is hydrogen or a lower alkyl, $R^3$ is a straight or branched $C_2$ - $C_6$ alkyl group, m is 1...30, and q is 1...3000.

13. The membrane or matrix according to Claim 12, **characterized** in that the free R' and R'' groups are lower alkyl groups, preferably methyl.

14. The membrane or matrix according to Claim 10 or 11, **characterized** in that the poly(alkylene oxide) groups are present in the straight-chain polysiloxane polymer in the form of poly(alkylene oxide) blocks having the formula

$-R^3O(\underset{R}{CHCH_2O})_mR^4-$, or

$-CH_2\underset{R_1}{CHCOO}(\underset{R}{CHCH_2O})_m\underset{R_1}{COCH}CH_2-$

where R is hydrogen, a lower alkyl or phenyl, $R_1$ is hydrogen or a lower alkyl, $R^3$ and $R^4$ are the same or different and are straight-chain or branched $C_2$ - $C_6$ alkyl groups, and m is 1...30.

15. The membrane or matrix according to Claim 10, **characterized** in that the siloxane-based elastomer is made up of poly(dimethyl siloxane).

16. The membrane or matrix according to any of Claims 10 - 15, **characterized** in that the siloxane-based elastomer

comprises poly(alkylene oxide) groups, and that the poly(alkylene oxide) groups are present in the elastomer or polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the said grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms.

17. The membrane or matrix according to any of Claims 1 - 16, **characterized** in that it contains a filler, suitably silica.

18. A method for the preparation of a siloxane-based elastomer which comprises poly(alkylene oxide) groups and is intended for use in a membrane or matrix controlling the permeation rate of drugs, **characterized** in that

a) a vinyl-functional polymer component and a hydride-functional component are crosslinked in the presence of a catalyst, or
b) a polymer component is crosslinked in the presence of a peroxide catalyst.

19. The method according to Claim 18, **characterized** in that the amounts of the vinyl-functional component and the hydride-functional component are selected so that the ratio of the molar amount of hydrides to the molar amount of double bonds is at minimum 1.

20. The method according to Claim 18 or 19, **characterized** in that
I) the vinyl-functional polymer component is

a) a vinyl-functional polysiloxane having the formula

R'-Sir'R''O(SiR'R''O)$_n$SiR'R''R'

where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the

said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, or

b) an alkenyl terminated polysiloxane-based block copolymer having the formula

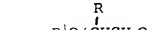
$T(AB)_xAT$ (I), where

A = $-(SiR'R''O)_qSiR'R''-$, where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

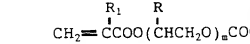
B is a poly(alkylene oxide) having the formula

$-R^3O(CHCH_2O)_mR^4-$, or

$-CH_2CHCOO(CHCH_2O)_mCOCHCH_2-$ and T is



$R^1O(CHCH_2O)_mR^3$, or



$CH_2{=}CCOO(CHCH_2O)_mCOCHCH_2-$

where R is hydrogen, a lower alkyl or phenyl, $R_1$ is hydrogen or a lower alkyl, $R^3$ and $R^4$ are the same or different and are straight-chain or branched $C_2$ - $C_6$ alkylene groups, $R^1$ is a straight-chain or branched $C_2$ - $C_6$ alkenyl group, m is 1...30, q is 1...3000, and x is 0...100, or

c) a vinyl-functional polysiloxane copolymer having the

formula

$$R'\text{-}SiR'R''O(SiR'R''O)_r(SiR'R''O)_pSiR'R''\text{-}R'$$

- where, in the first block, R' and R'' are the same or different and are a lower alkyl group, or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by vinyl groups, and r is 1...27000, and

- where, in the second block, R' is a lower alkyl group, or an alkoxy-terminated poly(alkylene oxide) group having the formula

$$-R^3\text{-}O\text{-}(\underset{\displaystyle R}{\underset{|}{CH}}\text{-}CH_2\text{-}O)_m\text{-}alk$$

where alk is a lower alkyl group, suitably methyl, $R^3$ is a straight or branched $C_2$ - $C_6$ alkyl group, R is hydrogen or a lower alkyl group, and m is 1...30, or R' is a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and R'' is a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and p is 1...5000, or

d) α,ω-dialkenyl poly(alkylene oxide) having the formula

$$R^1\text{-}O\text{-}(\underset{\displaystyle R}{\underset{|}{CH}}CH_2O)_m\text{-}R^2$$

where R is hydrogen or a lower alkyl, $R^1$ and $R^2$ are the same or different straight-chain or branched $C_2$ - $C_6$ alkenyl groups, and m is 1...30, or

e) a blend of at least two of the above-mentioned components a) - d), and that

II) the hydride-functional component is

a) a hydride-functional siloxane which may be straight-chain, star shaped, branched or cyclic, or

b) a hydride-terminated siloxane-based block copolymer having the formula

$T(BA)_xBT$ (II), where

T = H-SiR'R''O(SiR'R''O)$_q$SiR'R''-,
A = -SiR'R''O(SiR'R''O)$_q$SiR'R''-, where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted;

B is a poly(alkylene oxide) having the formula

$$-R^3-O(\underset{\displaystyle R}{\underset{|}{C}}HCH_2O)_mR^4-, \text{ or}$$

$$-CH_2\underset{\displaystyle R_1}{\underset{|}{C}}HCOO(\underset{\displaystyle R}{\underset{|}{C}}HCH_2O)_mCO\underset{\displaystyle R_1}{\underset{|}{C}}HCH_2-$$

where R is hydrogen, a lower alkyl or phenyl, $R_1$ is hydrogen or a lower alkyl, $R^3$ and $R^4$ are the same or different and are straight-chain or branched $C_2$ - $C_6$ alkyl groups, m is 1...30, q is 1...3000, and x is 0...100, or

c) a blend of the above-mentioned components a) and b).

21. The method according to Claim 20, characterized in that the hydride-functional siloxane copolymer is straight-chain, and that its formula is

R'-SiR'R''O(SiR'R''O)$_r$SiR'R''R'

where R' and R'' are the same or different and are a lower alkyl group or a phenyl group, in which case the said alkyl or phenyl group may be substituted or unsubstituted, and where some of the substituents R' and/or R'' have been substituted for by hydrogen, and r is 1...27000.

22. The method according to any of Claims 18 - 21, characterized in that the vinyl-functional polymer component contains a filler, suitably silica.

**ABSTRACT OF THE DISCLOSURE:**

A membrane or matrix for controlling the permeation rate of a drug, where the membrane or matrix includes a siloxane-based elastomer composition which contains at least one elastomer and possibly a non-crosslinked polymer. The elastomer composition includes poly(alkylene oxide) groups, and the poly(alkylene oxide) groups are present in the elastomer or the polymer as alkoxy-terminated grafts of polysiloxane units, or as blocks, the grafts or blocks being linked to the polysiloxane units by silicon-carbon bonds, or as a mixture of these forms. Methods for the preparation of the elastomer composition to be used in the membrane or matrix are also disclosed.

Docket No. _____

# Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled (INSERT TITLE) A membrane or matrix for controlling the permeation rate of drugs,
the specification of which

(Check one of 1, 2, or 3.)

1. _ is attached hereto.
2. X was filed on 11 June 1999 as International PCT Application Serial No. PCT/FI99/00511 and was amended on _____ (if applicable).
3. _ was filed on _____ as U.S. Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application for which priority is claimed:

| (List prior foreign applications.) | (Number) | (Country) | (Day/Month/Year Filed) | Priority Claimed |
|---|---|---|---|---|
| | 981506 | Finland | 30/06/98 | X Yes __ No |
| | | | | ___ Yes __ No |

___ See attached list for additional prior foreign applications

I hereby claim the benefit under Title 35, United States Code, §120, of any United States application listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

| (Application Serial No.) | (Filing Date) | (Status) |
|---|---|---|
| | | |

I hereby appoint as principal attorney James C. Lydon, Reg. No. 30,082.

Please direct all communications to the following address:

James C. Lydon
Attorney at Law
100 Daingerfield Road, Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first or sole inventor: Harri Jukarainen

Inventor's Signature: _____ Date: 13 November 2000

Residence: Tavastilankatu 6 A 5, FIN-20610, Finland FIX

Citizenship: Finnish

Post Office Address: same as residence

2-00

Full name of second inventor: Tommi Markkula
Inventor's Signature: [signature] Date: 20 November 2000
Residence: 26 St James Drive, Sale, Cheshire M33 7QX, United Kingdom GBX
Citizenship: Finnish
Post Office Address: same as residence

3-00

Full name of third inventor: Juha Ala-Sorvari
Inventor's Signature: [signature] Date: 13 November 2000
Residence: Ruonalankatu 12 as 3, FIN-20900 Turku, Finland FIX
Citizenship: Finnish
Post Office Address: same as residence

4-00

Full name of fourth inventor: Matti Lehtinen
Inventor's Signature: [signature] Date: 13 November 2000
Residence: Kirjosiéponkatu 2, FIN-20760 Piispanrisri, Finland FIX
Citizenship: Finnish
Post Office Address: same as residence

5-00

Full name of fifth inventor: Jarkko Ruohonen
Inventor's Signature: [signature] Date: 13 November 2000
Residence: Vanha Härkätie 10, FIN-21410 Vanhalinna, Finland FIX
Citizenship: Finnish
Post Office Address: same as residence

Full name of sixth inventor:
Inventor's Signature: Date:
Residence:
Citizenship:
Post Office Address:

Full name of seventh inventor:
Inventor's Signature: Date:
Residence:
Citizenship:
Post Office Address:

Full name of eighth inventor:
Inventor's Signature: Date:
Residence:
Citizenship:
Post Office Address: